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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,268	11/17/2003	Serengulam V. Govindan	018733-1317	1475
26633	7590	10/31/2005	EXAMINER	
HELLER EHRMAN WHITE & MCAULIFFE LLP			PONNALURI, PADMASHRI	
1717 RHODE ISLAND AVE, NW			ART UNIT	
WASHINGTON, DC 20036-3001			PAPER NUMBER	

1639

DATE MAILED: 10/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/713,268

Applicant(s)

GOVINDAN, SERENGULAM V.

Examiner

Padmashri Ponnaluri

Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 August 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-20 and 23-32 is/are pending in the application.
- 4a) Of the above claim(s) 14,15,26 and 27 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-13, 16-20, 23-25, 28-32 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

NOTE the change of examiner in this application.

1. The amendment and the response filed on 8/8/05 has been fully considered and entered into the application.
2. Claims 11-20 and 23-32 are currently pending in this application.
3. Claims 1415, 26-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/22/04.
4. Claims 11-13, 16-20, 23-25 and 28-32 are currently under consideration.

Priority (Intervening Reference)

5. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The present application (10/713,268: filed 11/17/03) claims 35 USC 120 priority:

- a. as a divisional of 09/605,873 (filed 6/29/00);
- b. which is a CIP of 08/919,477 (filed 8/28/97)

CIP of PCT/US97/23711 (filed 12/19/1997)

Art Unit: 1639

CIP of PCT/US97/14998 (filed 8/27/97).

Present claims 11-32 (including the election invention: claims 11-13, 16-20, 23-25, and 28-32) are entitled to 35 USC 120 to the date of filing of the 09/605,873 application (6/29/00).

However, NEW MATTER present in the present application which is necessary for both descriptive and enablement support i.e.

- (see present specification page 7, line 20-28 (6th embodiment presently claimed);
- page 10, line 23- page 11, line 21: improvement over DLT-embodiments of products synthesized by the presently claimed invention); and
- Example 16 (illustrating present syntheses and resulting compound)

Which is NOT present in the prior application recited in item B results in the DENIAL OF 35 USC 120 PRIORITY of the present claimed to the filing date of the applications recited in item b for failure to satisfy 35 USC 112/1.

Accordingly, for purposes of prior art, the present claimed invention is afforded the filing date of the immediate parent application (item a. above) e.g. 6/29/00.

Withdrawn Claim Rejections

6. The rejections of lack of antecedent basis in claims 23 and 25 have been withdrawn in view of the amendments to the claims.

Maintained Claim Rejection

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Art Unit: 1639

8. The rejection of claims 11 and 23 (and claims dependent thereon) under 35 U.S.C. 112, second paragraph, set forth in the previous office action has been maintained for the reasons of record.

9. The rejection of claims 11-13, 16-18, 23-25, and 28-30 under 35 U.S.C. 103(a) as being unpatentable over Strobel et al. Archives of Biochemistry and Physics, Vol. 240, No. 2 (Aug. 1985) pages 635-645 and Govindan et al., Bioconjugate Chem. Vol. 10 (2/99) pages 231-240, set forth in the previous office action has been maintained for the reasons of record.

10. The rejection of claims 11-13, 16-20, 23-25, and 28-32 under 35 U.S.C. 103(a) as being unpatentable over the Strobel and Govindan (Bioconjugate) references as applied to claims 11-13, 16-18, 23-25, and 28-30 above, and further in view of Govindan WO 99/11294 (3/99), set forth in the previous office action has been maintained for the reasons of record.

Response to Arguments

11. Applicant's arguments filed on 8/8/05, regarding the rejection of claims 11-13, 16-20, 23-25 and 28-32 under 35 USC. 112, second paragraph, have been fully considered but they are not persuasive.

Claims 11 and 23 (and claims dependent thereon) are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the attachment point of the "linking group" to the "carbohydrate-appended peptide".

Applicants argue that the examine fails to offer any reasoning as to why it is necessary to specify the location of the linker group.

Applicant's arguments are not persuasive, since the claimed method results in a carbohydrate-appended peptide, which used to radio-iodinating an antibody. The carbohydrate-

Art Unit: 1639

appended peptide of the instant claims comprises a linker, and the location or position of the linker is essential, since the carbohydrate appended peptide has to bind the antibody.

Applicants further argue that the linker could be attached to any suitable attachment point in the peptide. And further argue that 'to force applicants to specify a particular location of the linker would unfairly limit the scope of the applicants claims.'

Applicant's arguments have been considered and are not persuasive. The specification has not disclosed the attachment of the linker to any suitable point. The specification discloses the attachment to the amino end of the peptide. The specification has not disclosed that the linker is attached to the any other position or guidance to attach to any other point in the peptide. Thus, for the reasons of record the rejection has been maintained.

12. Applicant's arguments filed on 8/8/05, regarding the obviousness rejection of claims over Strobel et al and Govindan (Bioconjugate Chemistry); and the rejection of claims over Strobel et al and Govindan (Bioconjugate Chemistry) (Govindan I) and WO 99/11294 (Govindan II) have been fully considered but they are not persuasive.

NOTE the response has addressed both obviousness rejections of record together.

a) Claims 11-13, 16-18, 23-25, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strobel et al. Archives of Biochemistry and Physics, Vol. 240, No. 2 (Aug. 1985) pages 635-645 and Govindan et al., Bioconjugate Chem. Vol. 10 (2/99) pages 231-240.

The presently claimed invention is drawn to a method for producing a carbohydrate (CHO)-appended peptide useful for radio iodinating an antibody, comprising conjugating a radioiodinatable peptide to a CHO to form a CHO-appended peptide; wherein the CHO-appended peptide comprises

(a) a peptide that comprises at least one D-tyrosine, an amino terminus, a carboxy terminus formed from a D-lysine and no contiguous L-amino acids between the D-tyr and the carboxy terminus,

Art Unit: 1639

(b) a reducing CHO conjugated to the peptide via an ϵ -amino group of the D-lysine to form a CHO-appended peptide; and

(C) a linker group covalently binding said CHO-appended peptide to an antibody.

Thus, the presently claimed invention encompasses the reaction of:

(LINKER) - Gly-D-Tyr-D-Lys which is reductively coupled to a "reducing CHO" utilizing the side-chain of an ϵ -amino group of the D-lysine.

Product embodiments include:

MCC-Gly-D-Tyr-D-Lys-(dilactitol/melibiose)-OH;

Where the elected linker is MCC (4-N-maleimidomethyl-cyclohexane-1-carbonyl);

and the elected CHO is melibiose.

The Strobel et al. reference teaches a method of producing Iodinated glycoconjugate labels comprising conjugating a radioiodinatable amino acid (e.g. Tyrosine or tyramine) with a "reducing CHO" (e.g. dilactitol) with the presence of a linking moiety to a protein (e.g. antibody) present on the CHO or attached via the sidechain of the tyr or tyramine compound. SEE figure 2. The Strobel reference teaches that the protein (e.g. antibody) is coupled (e.g. to the CHO) via reductive amination but notes that "The ϵ -amino group of lysine residues is the likely site of attachment of glycoconjugates to protein by either coupling technique" (page 640, left column).

The Strobel et al. reference method for making a I-glycoconjugate labels (E.g. dilactitol- I^{125} tyr/tyramine: DLT, when the amino acid is tyramine) differ from that presently claimed by replacing the Tyr or tyramine portion of the Strobel conjugate with a peptide containing D-amino acids and an antibody linker e.g. (MCC)-Gly-Dtyr-Dlys.

However, the Govindan et al. reference teaches that the Strobel et al. residualizing glycoconjugate labels (e.g. DLT: see reference 7 cited in the Govindan reference on page 231, right column) are problematic (e.g. low radioiodine incorporation into antibodies resulting in low specific activities and a multistep antibody labeling procedure: see page 232, left column). In this regard, the Govindan reference teaches that utilizing a D-amino acid containing peptide comprising D-tyr (for iodination) and D-Lys (for ϵ -amino group coupling) and an amino terminal glycine attached to a linker (e.g. maleimide linker for antibody attachment) results in an improved residualized label. In this respect: the presence of D-amino acids renders the peptide bonds less susceptible to the

Art Unit: 1639

action of proteases in the lysosomes; with the N-terminal gly providing a means for coupling antibody. See e.g. Govindan at page 232, left column; abstract. More specifically, scheme 1, compound V is drawn to a thiolated MCC-Gly-Dtyr-Dlys.

One of ordinary skill in the art at the time of applicant's invention would be motivated to substitute the Linker-D amino acid containing Govindan peptide for Tyr/tyramine amino acid in the Strobel et al. reference conjugate and arrive at a method and product (e.g. MCC-Gly-D-Tyr-D-Lys-(dilactitol)-OH) which is within the scope of the presently claimed invention since:

- a. the Govindan and Strobel references are immediately combinable since the Strobel reference is cited by the analogous Govindan reference providing an explicit reference motivation to combine the teachings of both references;
- b. one of ordinary skill would be motivated to substitute the Govindan D-amino acid containing linker containing peptide for the Tyr or tyramine present in the Strobel DLT compound since the Govindan reference identifies the problems of the Strobel DLT compound (e.g. low radioiodine incorporation into antibodies resulting in low specific activities and a multistep antibody labeling procedure: see page 232, left column) and arrives at a solution e.g. utilizing D-amino acids to increase specific activity (e.g. less enzymatic degradation) and attach the antibody linker using a Gly-maleimide derivative thus permitting easier (e.g. less steps) antibody labeling.
- c. The Strobel reference further recognizes the use of reductive coupling using the ϵ -amino group side chain of lysine; which was incorporated in the Govindan peptide to permit thiolation but which would be useful for CHO attachment as recognized by Strobel and as utilized in the presently claimed invention.

Thus it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Strobel reference method to substitute the Govindan D-amino acid containing peptide with N-terminal Gly-linker (e.g. MCC-Gly-D-Tyr-D-Lys) for the Strobel amino acid tyr/tyramine for coupling to the Strobel reducing CHO (e.g. dilactitol) and arrive at the presently claimed method with a reasonable expectation of success of attaining a more residual/stable/entrapped glycoconjugate label (E.g. D-amino acids result in a more enzymatically stable label) with the further benefit of more efficient antibody labeling. fig. 2).

Art Unit: 1639

b) Claims 11-13, 16-20, 23-25, and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over the Strobel and Govindan (Bioconjugate) references as applied to claims 11-13, 16-18, 23-25, and 28-30 above, and further in view of Govindan WO 99/11294 (3/99).

The combined teaching of the Strobel and Govindan (Bioconjugate) references in the above 35 USC 103 rejection is hereby incorporated by reference in its entirety.

The combined Strobel/Govindan (Bioconjugate) reference method teaching differs from the presently claimed invention (e.g. claims 19-20 and 31-32) by choosing melibiose instead of lactose (e.g. dilactitol) as the reducing CHO to be conjugated to the amino acid or peptide.

However, Govindan WO 99 teaches the advantages of substituting melibiose for lactose utilized by Strobel e.g. in order to lessen aggregate formation and/or promote oxidation by galactose oxidases. See e.g. pages 5-6 (background citing Strobel) ; page 7; and pages 14-15.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to substitute melibiose for lactose in the combined method teaching of Strobel/Govindan (Bioconjugate) in order to optimize the glycoconjugate method and/or obtain more optimum glycoconjugate labels (e.g. to lessen aggregate formation and/or promote oxidation by galactose oxidases) with a reasonable expectation of success.

Applicants argue that the examiner has failed to set forth adequate reasons as to why one of ordinary skill in the art would have been motivated to combine the cited reference to arrive at the instantly claimed invention and therefore no prima-facie case of obviousness exists, and the rejection should be withdrawn.

Applicant's arguments are not persuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

Art Unit: 1639

See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as stated in the previous office action in page 8,

a) the Govindan and Strobel references are immediately combinable since the Strobel reference is cited by the analogous Govindan reference providing an explicit reference motivation to combine the teachings of both references;

b. one of ordinary skill would be motivated to substitute the Govindan D-amino acid containing linker containing peptide for the Tyr or tyramine present in the Strobel DLT compound since the Govindan reference identifies the problems of the Strobel DLT compound (e.g. low radioiodine incorporation into antibodies resulting in low specific activities and a multistep antibody labeling procedure: see page 232, left column) and arrives at a solution e.g. utilizing D-amino acids to increase specific activity (e.g. less enzymatic degradation) and attach the antibody linker using a Gly-maleimide derivative thus permitting easier (e.g. less steps) antibody labeling.

C) The Strobel reference further recognizes the use of reductive coupling using the ϵ -amino group side chain of lysine; which was incorporated in the Govindan peptide to permit thiolation but which would be useful for CHO attachment as recognized by Strobel and as utilized in the presently claimed invention.

Applicants further argue Strobel teaches use of a sugar-linked tyramine to radioiodinate proteins. Strobel does not, however, teach the use of peptide containing D-Tyr or D-Lys.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejection is based on

Art Unit: 1639

combined teachings of Strobel et al and Govindan et al, and the examiner has stated the why one skilled in the art would have reasons to substitute the Tyr or tyramine present in the peptide taught by Strobel et al with D-amino acids taught by Govindan et al, i.e., see page 8 of the previous office action: 'one of ordinary skill would be motivated to substitute the Govindan D-amino acid containing linker containing peptide for the Tyr or tyramine present in the Strobel DLT compound since the Govindan reference identifies the problems of the Strobel DLT compound (e.g. low radioiodine incorporation into antibodies resulting in low specific activities and a multistep antibody labeling procedure: see page 232, left column) and arrives at a solution e.g. utilizing D-amino acids to increase specific activity (e.g. less enzymatic degradation) and attach the antibody linker using a Gly-maleimide derivative thus permitting easier (e.g. less steps) antibody labeling.'

Applicants further seem to be arguing the individual reference Govindan (Govindan I) in the claimed rejection (page 8 of the response).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue that 'why would one of ordinary skill in the art, provided with improved methods described in Govindan, been motivated to somehow combine Strobel and Govindan, rather than utilize the ready-made improvements provided by Govindan?'

Applicant's arguments are not persuasive, since the instant claims are drawn to methods for producing a radio-iodinated carbohydrate-appended peptide. Strobel et al teach the methods

Art Unit: 1639

for producing iodinated glycoconjugates comprising conjugating radioiodinatable amino acid.

Govindan et al has not been used by the examiner as anticipatory reference since Govindan et al does not teach 'carbohydrate conjugated peptides.

Further, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicants further argue that 'Strobel clearly refers to the side chain of lysine residue on the protein to be conjugated and not any lysine in the Strobel conjugate, Applicant's methods use peptides containing a D-lysine that is used to covalently link a reducing sugar via the lysine side chain. The peptide is then conjugated to a protein via a distinct linker moiety. This conjugation approach is quiet different from that described in Strobel.'

Applicant's arguments have been considered and are not persuasive. Because as in applicant's response, applicants agree that Strobel et al teach the linking of carbohydrate group to the side chain of Lysine. Thus it is not clear what does applicants mean that the current conjugation approach is quiet different from the described in Strobel.

Applicants further argue Individual references Strobel and Govindan et al.

Applicant's arguments regarding the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

Art Unit: 1639

combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants argue that Govindan II is cited merely for the proposition that melibiose could be substituted for the dilaito described in Strobel. However, Govindan II fails to remedy the deficiencies of the combination of Strobel et al and Govindan II described above, and therefore the rejection of claims 11-13, 16-20, 23-25 and 28-32 also should be withdrawn.

Applicant's arguments are not persuasive for the reasons of record. Since the combined teachings of the references Strobel et al and Govindan I et al teach all the limitations of the claims, and the use of Govindan II was used only to address the limitations of claims 19-20 and 31-32. Thus, the rejections of record have been maintained for the reasons set forth in the previous office action and the reasons set forth in the response to the arguments set forth supra.

Conclusion

13. No claims are allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,


Art Unit: 1639

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809. The examiner is on Increased Flex Schedule and can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


PADMASHRI PONNALURI
PRIMARY EXAMINER

Padmashri Ponnaluri
Primary Examiner
Art Unit 1639

24 October 2005